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Association of omega-3/6 polyunsaturated fatty acids with three cerebrovascular diseases

A Mendelian randomization study

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Abstract

Nutritional and dietary interventions are important in the prevention of stroke, but many of the factors influencing stroke remain undefined. Although omega-3/6 polyunsaturated fatty acids (PUFAs) have been suggested to be associated with cerebrovascular diseases, studies on this topic are lacking. This study extracted and screened independent single nucleotide polymorphisms of omega-3/6 PUFAs and 3 types of cerebrovascular diseases data from the IEU Open GWAS database. A two-sample Mendelian randomization (MR) was used to examine the association between omega-3/6 PUFAs with subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), and ischemic stroke (IS). The primary analysis method was the inverse variance weighting method, supplemented by the weighted median and MR-Egger methods. Sensitivity and multiplicity were assessed using Cochran *Q* test, MR-PRESSO, MR-Egger regression, and leave-one-out analysis. This study was conducted in full compliance with the STROBE guidelines throughout. The inverse variance weighting analysis revealed a negative correlation between omega-3 PUFAs and SAH ($P = .0078$). However, there was no correlation between omega-3 PUFAs and ICH ($P = .3930$) and IS ($P = .2922$). Additionally, there was no association between omega-6 PUFAs and SAH ($P = .1399$), ICH ($P = .1399$, 0.0660), and IS ($P = .8571$) using all 3 analytical methods. No heterogeneity or horizontal pleiotropy was observed. The study suggested that omega-3 PUFAs had a significant protective role in SAH. However, omega-3/6 PUFAs were not found to be associated with other types of cerebrovascular diseases.

Abbreviations: GWAS = genome-wide association study, ICH = intracerebral hemorrhage, IS = ischemic stroke, IV = instrumental variable, IVW = inverse variance weighting, MR = Mendelian randomization, PUFAs = polyunsaturated fatty acids, SAH = subarachnoid hemorrhage, SNPs = single nucleotide polymorphisms.

Keywords: Mendelian randomization, metabolism, nutrition, omega unsaturated fatty acids, stroke

1. Introductions

Stroke is the most common acute cerebrovascular disease, comprising ischemic stroke (IS) and hemorrhagic stroke (parenchymal hemorrhage, subarachnoid hemorrhage, etc). Stroke is the second most common fatal disease worldwide,[1] and the number of stroke patients has increased by 70% from 1990 to 2019.[2] In recent years, there has been an increase in the incidence of stroke at a younger age. More than 2 million young people globally experience a stroke each year, and 1 in 4 adults will experience a stroke.[3] Research on stroke prevention is significant. Current studies have confirmed that stroke is associated with several factors, such as hypertension, diabetes, hyperlipidemia, smoking, and family history. However, there are still many unspecified factors influencing stroke.

Nutritional and dietary interventions are crucial for stroke prevention.[4] Although studies on omega-3 polyunsaturated fatty acids (PUFAs) and stroke are relatively rare, they have been shown to prevent and treat various cardiovascular diseases over the past few decades.[5,6] Omega-3 PUFAs have been validated in studies to inhibit inflammation, reduce obesity, lower blood pressure, and prevent cardiovascular and autoimmune diseases.[7–9] Hypertension and obesity, as well as inflammation, are significant factors in the occurrence and development of

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Ethical review and approval were not required for this study as all data used in this study are publicly available.

Supplemental Digital Content is available for this article.

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stroke.[10] Therefore, omega-3 PUFAs may be effective in reducing the incidence of stroke and delaying its progression in conditions such as subarachnoid hemorrhage (SAH), Intracerebral hemorrhage (ICH), and IS.[11] However, currently, there are no studies that provide a definitive answer regarding the relationship.[12] Similarly, there is no conclusive evidence that omega-6 fatty acids, which counteract omega-3, increase the likelihood of these strokes occurring.[13]

To investigate the relationship between omega PUFAs and stroke, we conducted a two-sample Mendelian randomization (MR) analysis using data from the Genome-Wide Association Study (GWAS). This analysis aimed to assess the potential relationship between omega-3 and omega-6 PUFAs and the risk of SAH, ICH, and IS. The MR approach is an epidemiological method that uses genetic variation as an instrumental variable (IV) to infer potential associations between exposures and outcomes.[14] Genetic variants are assigned randomly to a given allele during conception, similar to a randomized trial, and remain unchanged after sperm–egg binding. This allows MR studies to overcome the effects of confounders and reverse causation on causal inference.[15]

2. Methods

2.1. Study design

This study employed a two-sample MR design. The 3 fundamental assumptions for validated MR analyses are as follows: (i) the genetic IV is strongly associated with omega-3 and omega-6 PUFAs (association assumption); (ii) the genetic IV does not influence the outcome through confounding (independence assumption); and (iii) the genetic IV does not directly influence the outcome of the 3 types of strokes, but only through indirect exposure (exclusivity assumption).[16] Figure 1 presents an overview of the study design. The study utilized publicly available data from GWAS that had been approved by the relevant institutional review boards. Therefore, additional informed consent or ethical approvals were not required.

2.2. Data sources

Our study collected abstract data from publicly available GWAS sources to ensure the efficiency and rationality of our MR analyses. Single nucleotide polymorphisms (SNPs) associated with omega-3/6 PUFAs were extracted from the latest GWAS study data, which included 114,999 individuals of European ancestry. The GWAS data for SAH, ICH, and IS are based on the EBI 2021 release study. All of the aforementioned GWAS study data can be accessed at https://gwas.mrcieu.ac.uk/. For further information on the GWAS data used in this analysis, please refer to Tables S1 and S2, Supplemental Digital Content, https://links.lww.com/MD/O887.

The pooled GWAS data in this study had European ancestry in both the exposure and outcome groups, which reduces bias due to differences in genetic background. Furthermore, the sources were distinct between the exposure and outcome groups, and there was no significant sample overlap. The results can be interpreted and used with greater confidence due to their increased reliability and accuracy.

The dataset used in this study is publicly available, and ethical clearance was obtained from the relevant institutional review boards for each of the included GWAS studies. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[17]

2.3. Selection of IV

To fulfill the first hypothesis of MR, we selected SNPs that were closely related to omega-3 and omega-6 PUFAs ($P < 5 \times 10^{-8}$, $r^2 < 0.001$, genetic distance = 10,000 kb) at the genome-wide level. To satisfy the second MR hypothesis that genetic variation is independent of potential confounders, we queried the Phenoscanner database. We ensured that the selected SNPs were free from known confounders such as obesity and diabetes.[18,19] Finally, we calculated r^2 and the F statistic to assess the presence of weak instrumental variable bias for the selected instrumental variables. An F value >10 indicates the absence of weak instrumental variable bias.[20,21]

2.4. Statistical analysis of MR

We used two-sample MR to examine the relationship between omega-3 or omega-6 PUFAs and SAH, ICH, and IS, as well as their directionality. The study employed inverse variance weighting (IVW) as the primary analysis method, with weighted median and MR-Egger used as supplementary analyses. To establish causality, the study considered results of $P < .05$ for IVW analyses, and a positive or negative beta value for weighted median and MR-Egger analyses. Heterogeneity was assessed

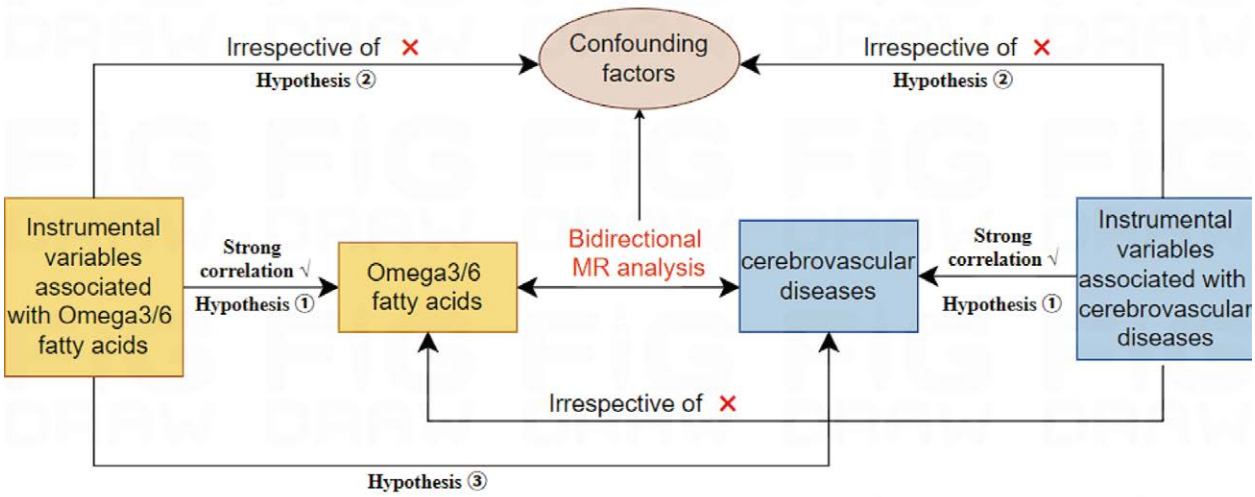

Figure 1. Mendelian randomization flow chart. MR = Mendelian randomization.

using Cochrane *Q* values. If no significant heterogeneity was found, we applied a fixed-effects IVW model. Otherwise, we used a random-effects IVW model. We verified horizontal pleiotropy using the MR-Egger intercept[22] and adjusted for potential pleiotropy using the MR-PRESSO method.[23] We also conducted omission analyses using the leave-one-out method, deleting 1 SNP at a time, to examine the effect of SNPs with potential horizontal pleiotropy on the MR estimates.[24] Finally, forest plots were used to assess the reliability and heterogeneity of chance estimates. Scatter plots were used to visualize the relationship between exposure and outcome, and funnel plots were used to assess whether the selected SNPs were roughly symmetric. The association between omega-3 or omega-6 PUFAs and different strokes was presented using odds ratios and 95% confidence intervals.[25] The procedures were performed using the TwoSampleMR and MR-PRESSO software packages with R software version 4.2.1.

3. Results

3.1. IV selection

A total of 50 independent SNPs for omega-3 PUFAs and 55 independent SNPs for omega-6 PUFAs were ultimately used as instrumental variables. The selected SNPs were identified as independent and their detailed information, including SNP identifiers, β coefficients, standard errors, and *P* values, can be found in Tables S1 and S2, Supplemental Digital Content, https://links.lww.com/MD/O887.

3.2. MR analysis of omega-3, omega-6 PUFAs associations for stroke

In this two-sample MR analysis, the potential impact of omega-3 on the development of SAH, ICH, and IS was assessed. The results were presented in Table 1 and Figure 2. Based on the random-effects IVW analysis, a 1 standard deviation increase in genetically predicted total omega-3 PUFAs levels was found to be associated with a reduction in the risk of SAH for each additional unit (odds ratio: 0.84311; 95% confidence interval: 0.74354–0.95601; *P*-IVW = 0.00778). The scatter plots in Figure 3 also indicate a negative association between total omega-3 PUFAs and SAH. Figures S1 and S2, Supplemental Digital Content, https://links.lww.com/MD/O888 show funnel plots and leave-one-out plots of genetic associations between omega-3 PUFAs and ICH and IS. In addition, the causal associations between omega-6 PUFAs and SAH, ICH, and IS were not significant using any of the 3 analytical methods.

3.3. Results of sensitivity analyses

Table 2 displayed the tests for pleiotropy and heterogeneity. The MR-PRESSO global test did not identify any outliers or horizontal pleiotropy in the results of the MR analysis (Table S3, Supplemental Digital Content, https://links.lww.com/MD/O887). Additionally, both IVW and MR-Egger were used in the *Q* test to detect heterogeneity, and no heterogeneity was found. Furthermore, the horizontal pleiotropy of genes was analyzed using MR-Egger regression. No horizontal pleiotropy was detected for the causal effect of PUFAs on hydrocephalus, based on the intercept value of MR-Egger regression. A leave-one-out stability test was performed by excluding 1 SNP at a time (refer to Figures S1 and S2, Supplemental Digital Content, https://links.lww.com/MD/O888). Estimates of potential associations between genetic prediction of omega-3 and omega-6 PUFAs and the risk of the 3 types of strokes remained consistent even after excluding 1 SNP at a time. This suggests that potential driver SNPs are unlikely to cause any causal bias. Please refer to Figures S1 and S2, Supplemental Digital Content, https://links.lww.com/MD/O888 for the funnel plots. Eventually, Table S4, Supplemental Digital Content, https://links.lww.com/MD/O887 summarized all the 5 data resources

Table 1

MR results for the relationship between omega-3/omega-6 fatty acids on cerebrovascular disease.

Exposure	Outcome	SNPs	*P*-value	OR	Low-95% CI	High-95% CI
Omega-3						
MR-Egger	SAH	50	.22968	0.89607	0.75087	1.06934
WM	SAH	50	.02439	0.84242	0.71997	0.98568
IVW	SAH	50	.00778	0.84311	0.74354	0.95601
Omega-3						
MR-Egger	ICH	50	.13246	0.86177	0.71228	1.04263
WM	ICH	50	.00769	0.82296	0.70682	0.95818
IVW	ICH	50	.29223	0.92961	0.81154	1.06485
Omega-3						
MR-Egger	IS	50	.89997	0.99457	0.91411	1.08213
WM	IS	50	.51681	0.98431	0.93839	1.03249
IVW	IS	50	.39297	0.97442	0.91817	1.03411
Omega-6						
MR-Egger	SAH	55	.64845	1.08035	0.77639	1.50332
WM	SAH	55	.42244	0.90005	0.69588	1.16414
IVW	SAH	55	.13992	0.88069	0.74397	1.04253
Omega-6						
MR-Egger	ICH	55	.88351	0.97381	0.68397	1.38647
WM	ICH	55	.17745	1.19235	0.92335	1.53971
IVW	ICH	55	.85712	1.01655	0.85024	1.21538
Omega-6						
MR-Egger	IS	55	.45533	0.94812	0.82521	1.08935
WM	IS	55	.26834	0.95525	0.87989	1.03707
IVW	IS	55	.06604	0.93663	0.87347	1.00435

All statistical tests were two-sided. $P < .05$ was considered significant.

CI = confidence interval, ICH = intracerebral hemorrhage, IS = ischemic stroke, IVW = inverse variance weighted, nSNP = number of single nucleotide polymorphisms, OR = odds ratio, SAH = subarachnoid hemorrhage.

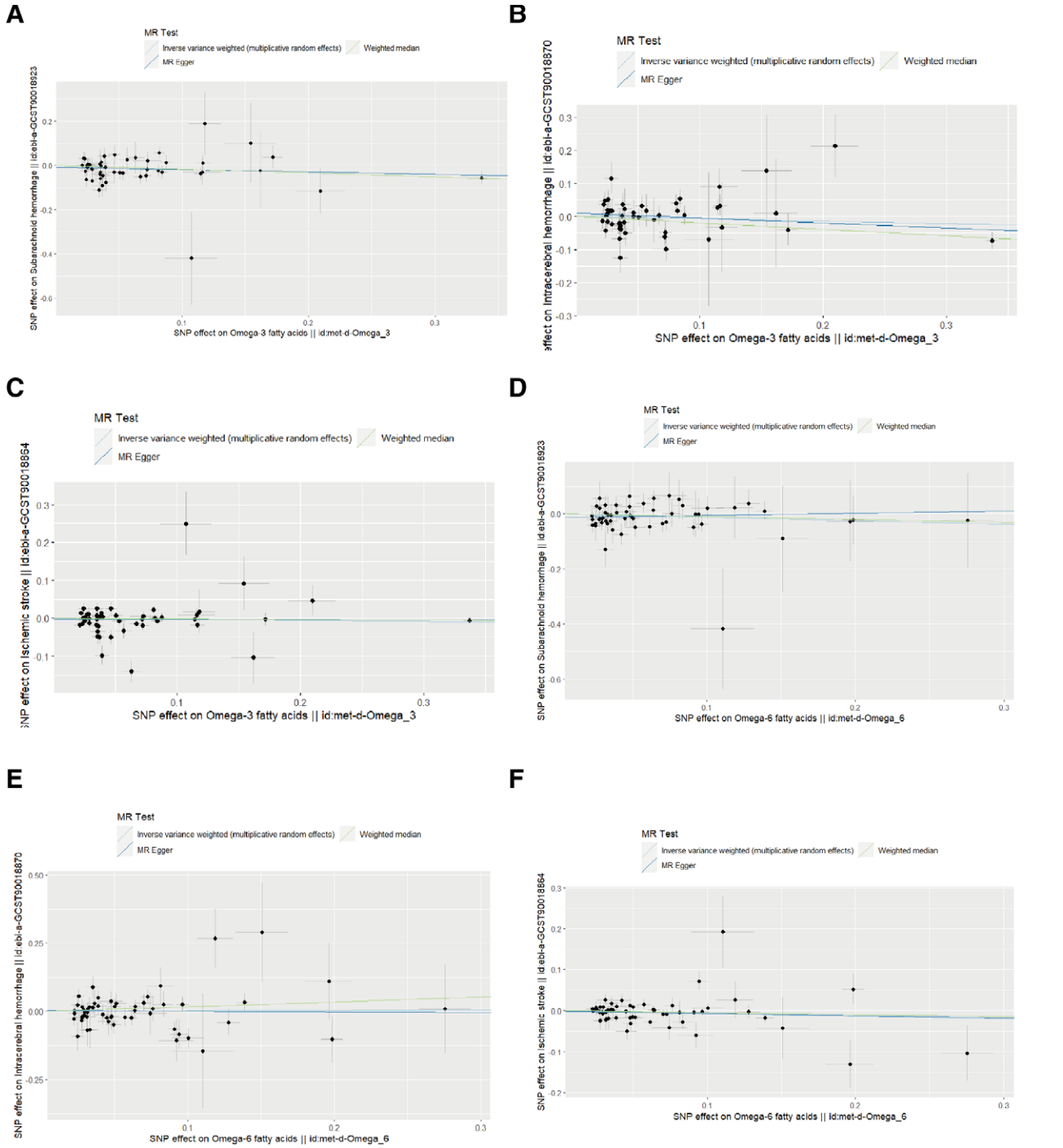

Figure 2. Forest plots of Mendelian randomization analysis. (A) Forest plots of omega-3 on SAH. (B) Forest plots of omega-3 on ICH. (C) Forest plots of omega-3 on IS. (C) Forest plots of omega-6 on SAH. (D) Forest plots of omega-6 on ICH. (E) Forest plots of omega-6 on IS. ICH = intracerebral hemorrhage, IS = ischemic stroke, MR = Mendelian randomization, SAH = subarachnoid hemorrhage.

of GWAS statistics about SAH, ICH, IS, omega-3 PUFAs, and omega-6 PUFAs.

4. Discussion

Stroke is a leading cause of mortality and disability worldwide. SAH, ICH, and IS are common cerebrovascular events. In recent years, there has been increasing attention on the role of omega-3 and omega-6 PUFAs in stroke due to advances in nutritional and medical research.[26] These 2 fatty acids are important components of cell membranes and have a significant impact on the structure and function of the nervous system.[27] Therefore, it is important to conduct an in-depth investigation of the molecular mechanisms involved in stroke for its prevention and treatment.[28,29]

Using MR methods, we analyzed the causal relationship between omega-3 and omega-6 PUFAs and 3 types of stroke. Our findings indicate a negative association between omega-3 fatty acids and SAH, while no association was found between omega-3 PUFAs and cerebral hemorrhage or cerebral ischemic infarction. Our study found no correlation between omega-6 and these 3 strokes. These findings could provide new insights into the treatment and prevention of SAH, ICH, and IS.

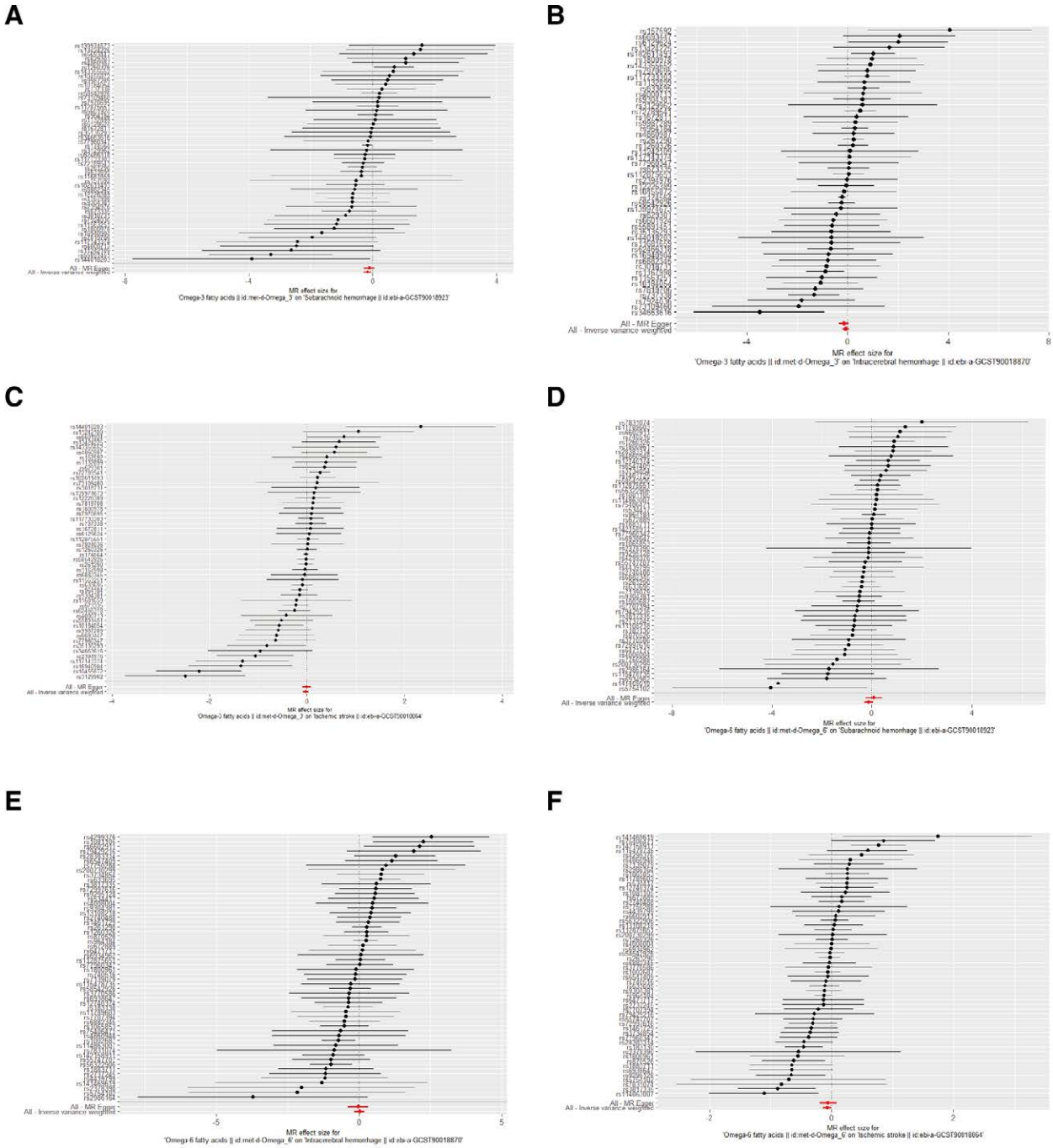

Figure 3. Scatter plots of Mendelian randomization analysis. (A) Scatter plots of omega-3 on SAH. (B) Scatter plots of omega-3 on ICH. (C) Scatter plots of omega-3 on IS. (D) Scatter plots of omega-6 on SAH. (E) Scatter plots of omega-6 on ICH. (F) Scatter plots of omega-6 on IS. ICH = intracerebral hemorrhage, IS = ischemic stroke, MR = Mendelian randomization, SAH = subarachnoid hemorrhage, SNP = single nucleotide polymorphisms.

Omega-3 and omega-6 PUFAs are 2 important classes of PUFAs that have a significant impact on human health. They are involved in a variety of physiological and pathological processes in the body, such as cell signaling, inflammatory responses, and gene expression.[30–32] However, if the body consumes an excess of omega-6 PUFAs and insufficient omega-3 PUFAs, negative effects may occur, such as an excessive inflammatory response and increased oxidative stress. These effects may increase the risk of stroke.[33]

SAH is a severe type of stroke that is primarily caused by the rupture of intracranial aneurysms. Studies have identified hemodynamic shock and inflammatory changes in the arterial wall as the 2 most important factors contributing to the growth and rupture of intracranial aneurysms.[34] Additionally, omega-3 PUFAs have been found to have anti-inflammatory effects through 2 main mechanisms. Omega-3 PUFAs have 2 main benefits. Firstly, they produce specific pro-soluble lipid mediators such as lysins and protectins, which have anti-inflammatory effects. Secondly, they stimulate relaxation of vascular endothelial cells and block platelet activation by inhibiting reactive oxygen species production and neutrophil function.[35,36] Studies have confirmed that omega-3 PUFAs can treat abdominal aortic aneurysms.[37] However, there is a lack of research on the effects of omega-3 PUFAs on intracranial aneurysms. Our study is the first to verify that omega-3 PUFAs can reduce SAH. This may be due to their ability to reduce the growth and rupture

Table 2

The heterogeneity and sensitivity of omega-3/omega-6 fatty acids and cerebrovascular disease after removal unqualified IVs.

		MR-Egger intercept		Cochran heterogeneity			
Exposure–outcome	nSNP	Intercept value	*P*-value	IVW-*Q* value	*P*-value (IVW)	Egger-*Q* value	*P*-value (Egger)
Omega-3–SAH	50	-0.007473386	.3412418	57.30644	.1942418	56.22412	.1940942
Omega-3–ICH	50	0.00932123	.2729322	77.22329	.006198	75.29388	.007151816
Omega-3–IS	50	-0.00256406	.5035162	128.1340	5.300860e	126.9326	4.707002e
Omega-6–SAH	55	-0.01362281	.164321	46.82750	.775507	44.83986	.8083180
Omega-6–ICH	55	0.002860812	.7828584	70.73811	.074983	70.63776	.06379669
Omega-6–IS	55	-0.00080745	.8423967	89.94825	.002050	89.88181	.001568340

ICH = intracerebral hemorrhage, IS = ischemic stroke, IVW = inverse variance weighted, IVW = inverse variance weighted, MR = Mendelian randomization, nSNP = number of single nucleotide polymorphisms, SAH = subarachnoid hemorrhage.

of intracranial aneurysms. Furthermore, our study found no association between omega-6 PUFAs and SAH. Additionally, omega-6 PUFAs did not demonstrate significant anti-inflammatory effects, and excessive intake may exacerbate inflammatory responses and oxidative stress.[38]

It is important to note that ICH is a hemorrhagic stroke caused by the rupture of blood vessels in the brain parenchyma. There is a limited body of research on the relationship between omega-3 PUFAs and cerebral hemorrhage, and the results have been conflicting.[39,40] In contrast, omega-6 fatty acids have not been found to play a role in ICH. Our study found no association between omega-3 or omega-6 PUFAs and cerebral hemorrhage.

IS is a condition caused by inadequate blood supply to the brain due to blockage of blood vessels in the brain. Although some studies suggest that omega-3 PUFAs can reduce the risk of IS,[41] this conclusion is controversial. Two meta-analyses, which included 48 randomized controlled studies, concluded that omega-3 PUFAs do not reduce the incidence of IS.[11,42] This may be due to the complex nature of the effect of omega-3 PUFAs on stroke, which is influenced by factors such as ethnicity and intake.[43] In contrast, most studies have concluded that omega-6 PUFAs do not protect against cerebral IS and that excessive intake may increase the risk of cardioembolic stroke. However, moderate intake may have a positive effect on neural repair and functional recovery.[44,45]

Observational studies may be influenced by various confounding factors such as prior vulnerability to environmental influences, immune responses, and genetic variation. Conducting large-scale randomized controlled trials in clinical settings can be challenging, and the risk of bias in nutrition-related randomized controlled studies is relatively high. This study addressed the limitations of observational studies by using MR to minimize the interference of potential confounding factors. To reduce the impact of biased results due to ethnicity, we searched for publicly available GWAS data and selected a large sample size of European populations with relevant exposures and diseases. We also performed tests for heterogeneity and horizontal diversity. When heterogeneity was present, a random-effects model was chosen for the analysis of the results. Additionally, no evidence of pleiotropic effects was found. Finally, sensitivity analyses using the leave-one-out method confirmed the robustness and reliability of the MR results. MR studies have advantages in studying etiology in epidemiology because they are not subject to ethical considerations and economic constraints. The analysis results provide compelling evidence supporting the importance of omega-3 PUFAs as protective factors for SAH.

It was important to note that our MR study had limitations, as it only included exposures and outcomes in a European population, which may limit the generalizability of the findings to other ethnic populations. Additionally, due to objective constraints, the GWAS data we extracted did not include subgroup analyses that took into account factors such as sex, age, and medical history of the subjects. It is expected that the reliability of the results can be improved in the future with IVs obtained from more finely stratified data. This will be the direction of subsequent studies.

In summary, a two-sample MR approach was used to assess the causal relationship between omega-3 and omega-6 PUFAs and SAH, ICH, and IS. MR studies have confirmed that omega-3 plays an important protective role in SAH. The present study did not find any relationship between omega-3 PUFAs, omega-6 PUFAs and other types of stroke, which requires further verification through additional trials. Regulating the intake and metabolism of these 2 fatty acids may provide new strategies for stroke prevention and treatment. Testing the levels of PUFAs biomarkers in humans could support the diagnosis of cardio-stroke.[46] Future studies should explore the specific mechanism of action of these fatty acids in stroke and conduct relevant clinical trials to verify their value in clinical practice.

5. Conclusion

Our study revealed that omega-3 PUFAs exhibited a protective effect against cerebrovascular diseases, specifically reducing the risk of SAH. However, this protective effect was not observed for ICH or IS. Additionally, our findings did not establish any causal relationship between omega-6 PUFA levels and the 3 cerebrovascular diseases at the genetic level. This result may help us to treat or prevent patients or potential patients with SAH. We need to continue to explore the potential mechanism of PUFAs acting in cerebrovascular diseases.

Author contributions

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Formal analysis: Caiyun Jiao.
Funding acquisition: Haibing Xiong.
Investigation: Haibing Xiong, Xin Guo.
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Project administration: Letai Li, Shi Zeng.
Writing – original draft: Haibing Xiong, Letai Li, Yingjiu Jiang.
Writing – review & editing: Haibing Xiong, Letai Li, Yingjiu Jiang.

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